UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JN

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/475,470	06/07/95	SAMULSKI R	115132-4

HM22/0302

ARNOLD B. SILVERMAN
ECKERT SEAMANS CHERIN & MELLOTT
600 GRANT STREET, 42ND FLOOR
PITTDBURGH PA 15219

EXAMINER	
MOSHER, M	

ART UNIT	PAPER NUMBER
1643	27

DATE MAILED: 03/02/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/475,470	Applicant(s) Samulsi et al
	Examiner Mosher	Group Art Unit 1643

☒ Responsive to communication(s) filed on *12/9/98* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-47* is/are pending in the application.

Of the above, claim(s) *36-38 and 40-45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35, 39, 46, and 47* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1643, examiner Mosher.

Transitional After Final Practice

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on December 9, 1998 has been entered.

Election/Restriction

Claims 36-38 and 40-45 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12.

Claim Objections

The numbering of claims is not accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 40 and 40 have been renumbered as claims 46 and 47.

Claims 2- 3, 19, 34, 35 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 2 and 3 do not further limit claim 1, because claim 1 itself requires a eukaryotic based cis-acting regulatory sequence and a eukaryotic based nucleic acid sequence. Claims 34 and 35 expand, rather than limit, the scope of parent claim 27, because the RSV promoter region required in claims 34 and 35 does not meet the limitation of "regulating cell specific expression" as recited in claim 27. Claim 19 fails to further limit claim 18, because the choice of target cell in claim 19 does not further alter the metes and bounds of the specific vector construct set forth in claim 18.

Applicant is advised that should claims 1, 4, 7-9, 17, 18, 20, and 21 be found allowable, claims 2, 3, 5, 6, 10-16, 19, 22-24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 1-3 are identical in scope, since claims 2-3 merely reiterate elements already present in claim 1. Therefore claims 5-6, 10-16, 22-24 are substantial duplicates of claims 4, 7-9, 20-21 respectively. Claims 28 and 29 are substantial duplicates of claims 7 and 8; although claims 7 and 8 depend from claims requiring the control element to function specifically in a human immune cell, and claims 28 and 29 depend from a claim requiring the element to

function specifically in a human hematopoietic cell, both sets of claims require the identical control elements and therefore are identical in scope. Since claim 19 covers the same vector as claim 18, claim 19 is a substantial duplicate of claim 18.

Claim Rejections - 35 USC § 112

Claims 1-6, 27, 33, 39, 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention, or in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the full scope of the invention. Claims 1-6, 27, 33, and 39 require a "cis-acting regulatory sequence... having the property of regulating cell specific expression...[in a] target mammalian cell". The specification teaches the characteristics of one such set of regulatory sequences, the hypersensitive sites I-IV associated with the human globin gene cluster, which apparently regulate expression specifically in hematopoietic and immune cells. These cis-acting sites are known to be very small, less than 100 bases each. However, the broad claims encompass any and all sequences which act in cis for cell-specific expression, including specific expression in "human immune cells" (encompassing hematopoietic stem cells, myeloid progenitor cells, and erythroid progenitor cells, see claim 19). Because adeno-associated virus vectors are only capable of packaging about 4,000-5,000 bases of DNA, there are severe constraints upon the size of the cis-acting elements and the wild-type gene product which can be used in the vector. The

specification provides no guidance as to how to obtain any other cell-specific regulatory elements which are sufficiently small in size to be used with a coding sequence in AAV. Because the specification provides the physical characteristics of only one set of cell-specific cis-acting regulatory sequences which can perform the function recited in the claims, it is apparent that applicants were not in possession of a range of species representative of the full genus of cell-specific regulatory elements. Because of the limited guidance in the specification, the state of the art for small, cell-specific regulatory elements, and the limited scope of the working examples, it is concluded that both written description and enablement are limited to the HS I-IV sites associated with the human globin gene cluster.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-16, 20-29, and 46-47 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Srivasta 5,252,479. See Example 6.

Claim Rejections - 35 USC § 103

Claims 1-29, 46, and 47 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Walsh et al (1991). The claims have been amended to require a sequence that "encodes a wildtype gene product". Walsh et al teaches a recombinant AAV vector which contains globin gene "mutationally marked to allow its transcript to be distinguished from the native gamma globin mRNA in an RNASE protection assay.". The reference is silent upon whether or not this transcriptional marker had any affect on the gene product encoded by vector. If the marker was a deletion in the 5' untranslated region (like applicant's construct on specification page 24), then the reference vector encoded a wild type gene product, thereby anticipating the invention as claimed. Alternatively, considering that the Walsh et al abstract reported successful tissue-specific, regulated expression of a marked globin gene, one would have reasonably expected success in achieving similar expression of a wild-type globin gene. The invention as a whole is therefore prima facie obvious, absent unexpected results, if not anticipated. It is noted that Walsh et al do not state that the vector has the property of regulating cell specific expression upon stable transduction of a human hematopoietic cell; however it appears that the site II element inherently possesses this property, therefore recitation of this property does not distinguish the claim over the prior art.

Claims 30-32 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh et al (1991), for essentially the same reasons as given in paper no. 8.

Claims 33-35 are rejected under 35 U.S.C. 102(b) as being unpatentable over Walsh et al (1993), for essentially the same reasons as given in paper no. 8.

Response to Arguments

In applicant's response, applicant argues that the present invention "demonstrates for the first time an adeno-associated virus engineered to express a wild-type gene under the control of cis-acting regulatory elements which is capable of transducing a target mammalian host cell, integrate the host cell genome and stably express the wildtype gene in vivo for a prolonged period of time, thus effecting a change in the phenotype of the host cell." Applicant is invited to point to the disclosure of stable expression for a prolonged period of time for the ***cell-specific*** expression claimed. Note that working examples II and III used constitutive viral promoters (CMV IE, TK, or RSV LTR promoters). The 132 declaration of Dr. Samulski is silent upon which cis-acting regulatory sequence was used in the transplantation study; therefore it is not clear how the *in vivo* transplantation results relate to the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Eisenschenk, can be reached on (703) 308-0452. The fax phone number for this Group is now (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196 .

February 27, 1999

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1200~~ 1600